REMARKS

Claims 1-30 and 32-36 are pending in the application. Claim 1-21, 30 and 31-36 have previously been withdrawn from consideration as directed to a non-elected invention and are canceled herein. Claims 22-29 are presently under examination. Claim 22 has been amended to incorporate the elements of dependent claims 24-26, which have been canceled herein. No new matter has been introduced by the amendments and entry is respectfully requested. Upon entry of the amendment, claims 22, 23, and 27-29 will be pending and under examination.

Regarding the Claim Objections

Claim 24 has been canceled, rendering the rejection moot. Applicants respectfully request removal of the claim objections.

Regarding 35 U.S.C. § 112, First Paragraph

Written Description

Applicants traverse the rejection of claims 22 to 29 under 35 U.S.C. § 112, first paragraph, as lacking written description of the claimed invention sufficient to show that the inventors were in possession of the invention at the time the application was filed. The rejection has been rendered moot with regard to claims 24 to 26, which have been canceled herein.

As amended, base claim 22 is directed to a method of identifying a therapeutic agent for treating Alzheimer's disease by performing matings between a first parent strain carrying a mutation in an Alzheimer's disease gene selected from the group consisting of amyloid precursor protein-like (Appl), presenilin (Psn), halothane resistant (har38), cAMP-responsive element-binding protein A (CrebA), cAMP-responsive element-binding protein B (CrebB), α-adaptin, garnet, shibire (shi), Notch (N), Suppressor of Hairless (Su(H)), Delta (Dl), mastermind (mam) and big brain (bib) and a second parent strain containing a genetic variation, whereby test progeny are produced, where, in the absence of an agent, the parent strains produce test progeny having an altered phenotype relative to at least one sibling control; administering an agent to at least one strain selected from the group consisting of the first parent strain, the second parent strain and the test progeny; and assaying the test progeny for the altered phenotype, wherein a

modification of the altered phenotype producing a phenotype with more similarity to a wild type phenotype than the altered phenotype has to the wild type phenotype indicates that the agent is a therapeutic agent.

The specification discloses numerous Alzheimer's disease genes with which one skilled in the art can practice the invention and further provides additional exemplary Alzheimer's disease genes, including genes disclosed in the specification itself as interacting (directly or indirectly) with *Appl*. Additional Alzheimer's disease genes that are disclosed in the specification, for example at page 14, as useful for practicing the methods of the invention include, for example, *Notch* (N), *Suppressor of Hairless* (Su(H)), *Delta* (Dl), *mastermind* (mam), *big brain* (bib), *halothane resistant* (har38), *cAMP-responsive element-binding protein A* (CrebA), *cAMP-responsive element-binding protein B* (CrebB, activator), *cAMP-responsive element-binding protein B* (CrebB, inhibitor), *α-adaptin*, *garnet* (δ-adaptin), and *shibire* (shi)(dynamin). The specification teaches that an Alzheimer's disease gene can be a gene that is differentially expressed at the mRNA or protein level in $Appl^{d}$ flies as compared to $Appl^{+}$ flies and discloses several dozen specific examples of such Alzheimer's disease genes in Tables 4-6. One skilled in the art would have appreciated that Applicants were in possession of parental strains other than the Drosophila $Appl^{D}$, in sufficient numbers to show possession of the genus of parent strains that carry a mutation in an Alzheimer's disease gene.

The Examiner argues that there is no evidence of record or in the prior art at the effective filing date of the present application indicating that any mutation of the above genes, including their homologs and/or orthologs is associated with the Alzheimer s disease, specifically capable of producing the pathological features of the Alzheimer s disease characterized by the presence of extracellular amvloid deposits in specific brain regions.

The Examiner relies on support by various cited references that allegedly show the state of the art as well as the unpredictability of the prior art, particularly with respect to the attainment of any desired phenotype for a *transgenic* organism, in this instance an altered and relevant phenotype associated with Alzheimer s relevant useful in the claimed screening method for identifying a therapeutic agent for treating Alzheimer s disease. This assertion is respectfully submitted to be irrelevant to claim 22, which recites *performing matings between parent strains*

and is not directed to a transgenic organism. A transgenic organism is a type of genetically modified organism that has genetic material from another species.

The Examiner alleges that, apart from certain mutations as taught at least by Duff et al. and Mucke et al., there is no correlation between many of the above disclosed genes with a phenotype associated with Alzheimer s disease. As previously pointed out, the written description jurisprudence does not require corroborating third party publications nor is it possible to prove a negative, in this case, whether the Examiner's search has revealed all published materials that may or may not support a correlation. This is not part of the written description inquiry.

Finally, the Examiner's assertion that the instant specification fails to teach or describe fully the essential characteristics or elements possessed by a representative number of species for a broad genus of a first parent strain and a second parent strain, the claims have been amended such that base claim 22 is recites a Markush group of species. Accordingly, the claims are not directed to a broad genus.

With regard to the references provided by the Examiner directed to transgenic techniques, while not conceding lack of written description for transgenic methods, Applicants point out that, as taught in the specification, while the methods of the invention are exemplified using the genetic system Drosophila, any genetic system *suitable for transmission genetics and convenient analysis of test and sibling control progeny* is useful for practicing the methods of the invention (page 17, lines 1-10). In this regard, the specification further describes that examples of genetic systems suitable for practicing the methods of the invention include, for example, mice (*Mus musculus*), zebrafish (*Danio rerio*), nematodes (*Caenorhabditis elegans*), and yeast (*Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*)(page 17, lines 1-10). Therefore, the specification explicitly teaches that the invention methods are contemplated to be practiced via transmission genetics such that the issue of enablement of transgenic methods is tangential to the enablement of the claimed methods. Furthermore, claim 22 recites *matings* between the parent strains. Applicants respectfully submit that the specification conveys to the skilled person that, at the time of filing, Applicants had possession of the claimed methods of identifying a therapeutic agent for treating Alzheimer's disease.

The Examiner alleges that the skilled person cannot envision altered phenotypes that may be observed in the progeny. Applicants submit that the specification teaches a variety of behavioral, morphological and other physical phenotypes useful in the methods of the invention including *Drosophila* phenotypes such as eye color, wing shape, bristle appearance, size, phototaxis and viability. Additional phenotypes useful for practicing the invention that are taught in the specification include the size, viability, eye color, coat color, or exploratory behavior of mice; the size, viability, skin color, or optomotor response of zebrafish; the size, viability, phototaxis or chemotaxis of nematodes; and the colony color, colony size or growth requirements of yeast.

Further with regard to observable phenotypes, the specification teaches that viability is particularly useful for establishing a functional interaction between genes. Example I supports this teaching by demonstrating that flies carrying a combination of $Appl^{d}$ and the chromosomal deficiency Df(1)N8, Df(1)JC19, 9Df(1)ct4bl, Df(1)lz-90b24 or Df(1)HF396 had significantly decreased viability as compared to sibling controls, while flies carrying $Appl^{d}$ and the chromosomal deficiency Df(1)JF5, Df(1)2/19B or Df(1)RK2 had significantly increased viability as compared to sibling controls. With regard to a behavioral phenotype, Example III, shows that $Appl^{d}$ Drosophila have a defect in fast phototaxis and the specification teaches that such a behavioral phenotype can be useful in the methods of the invention for establishing a functional interaction as is disclosed herein for Appl and Notch, Delta, α-adaptin, dCrebA and dCrebB. The specification further teaches, for example, at page 24, that altered phenotypes are represented by a significant change in the physical appearance or observable properties of the test progeny as compared to a sibling control and can be identified by sampling a population of test progeny and determining that the normal distribution of phenotypes is changed, on average, as compared to the normal distribution of phenotypes in a population of sibling controls. *See also* Example I.

In view of the above arguments, Applicants respectfully request removal of the rejection of claims 22 to 29 under 35 U.S.C. §112, first paragraph, as lacking written description of the claimed invention sufficient to show that the inventors were in possession of the invention at the time the application was filed.

Enablement

Applicants traverse the rejection of claims 22 to 29 under 35 U.S.C. § 112, first paragraph, as lacking enablement of the claimed invention sufficient to teach a skilled person to perform the claimed methods at the time the application was filed. According to the Examiner, while being enabling for a method of identifying a therapeutic agent for treating Alzheimer s disease using progenies of art-recognized transgenic mouse models for Alzheimer s disease, the specification does not reasonably provide enablement for other embodiments of a method for identified a therapeutic agent for treating Alzheimer disease as claimed. The rejection has been rendered moot with regard to claims 24 to 26, which have been canceled herein.

The specification teaches a variety of behavioral, morphological and other physical phenotypes useful in the methods of the invention including *Drosophila* phenotypes such as eye color, wing shape, bristle appearance, size, phototaxis and viability. Additional phenotypes useful for practicing the invention that are taught in the specification include the size, viability, eye color, coat color, or exploratory behavior of mice; the size, viability, skin color, or optomotor response of zebrafish; the size, viability, phototaxis or chemotaxis of nematodes; and the colony color, colony size or growth requirements of yeast.

The specification teaches that viability is an observable phenotype particularly useful for establishing a functional interaction between genes. Example I supports this teaching by demonstrating that flies carrying a combination of *Appl*^{d} and the chromosomal deficiency Df(1)N8, Df(1)JC19, 9Df(1)ct4bl, Df(1)lz-90b24 or Df(1)HF396 had significantly decreased viability as compared to sibling controls, while flies carrying *Appl*^{d} and the chromosomal deficiency Df(1)JF5, Df(1)2/19B or Df(1)RK2 had significantly increased viability as compared to sibling controls.

With regard to a behavioral phenotype, Example III, shows that Appl^{d} Drosophila have a defect in fast phototaxis and the specification teaches that such a behavioral phenotype can be useful in the methods of the invention for establishing a functional interaction as is disclosed herein for Appl and Notch, Delta, α-adaptin, dCrebA and dCrebB. The specification further teaches, for example, at page 24, that altered phenotypes are represented by a significant change in the physical appearance or observable properties of the test progeny as compared to a sibling

control and can be identified by sampling a population of test progeny and determining that the normal distribution of phenotypes is changed, on average, as compared to the normal distribution of phenotypes in a population of sibling controls. *See also* Example I.

With regard to the references provided by the Examiner directed to transgenic techniques, while not conceding non-enablement of transgenic methods, Applicants point out that enablement of every single embodiment within the scope of the claims is not a prerequisite for the enablement of the claimed methods. As taught in the specification, while the methods of the invention are exemplified using the genetic system Drosophila, any genetic system *suitable for transmission genetics and convenient analysis of test and sibling control progeny* is useful for practicing the methods of the invention (page 17, lines 1-10). In this regard, the specification further teaches that examples of genetic systems suitable for practicing the methods of the invention include, for example, mice (*Mus musculus*), zebrafish (*Danio rerio*), nematodes (*Caenorhabditis elegans*), and yeast (*Saccharomyces cerevisiae* and *Schizosaccharomyces pombe*)(page 17, lines 1-10). Therefore, the specification explicitly teaches that the invention methods are contemplated to be practiced via transmission genetics such that the issue of enablement of transgenic methods is tangential to the enablement of the claimed methods. Furthermore, claim 22 recites *matings* between the parent strains. Applicants respectfully submit that the specification conveys to the skilled person that, at the time of filing, Applicants had possession of the claimed methods of identifying a therapeutic agent for treating Alzheimer's disease.

In view of the above arguments, Applicants respectfully request removal of the rejection of claims 22 to 29 under 35 U.S.C. §112, first paragraph, as allegedly failing to teach the skilled person how to perform the claimed methods at the time of the invention.

Regarding 35 U.S.C. § 102

Applicants respectfully traverse the separate rejections of claims 22-23, 25 and 28 under 35 U.S.C. § 102(e) as allegedly being anticipated by Mucke et al., U.S. Patent No. 6,455,757 and, under 35 U.S.C. § 102(b), as allegedly being anticipated by Duff et al., WO 98/17782. Both rejections have been rendered moot by incorporation of non-rejected dependent claims 24-26 into base claim 22. Accordingly, removal of the rejection of claims 22-23, 25 and 28 under 35

U.S.C. § 102(e) as allegedly being anticipated by Mucke et al., U.S. Patent No. 6,455,757, is respectfully requested. Similarly, removal of the rejection of claims 22-23, 25 and 28 under 35 U.S.C. § 102(e) as allegedly being anticipated by Duff et al., WO 98/17782, is respectfully requested.

CONCLUSION

In light of the amendments and remarks herein, Applicants submit that the claims are now in condition for allowance and respectfully request a notice to this effect. The Examiner is invited to call the undersigned attorney if there are any questions.

To the extent necessary, a petition for an extension of time under 37 C.F.R. 1.136 is hereby made. Please charge any shortage in fees due in connection with the filing of this paper, including extension of time fees, to Deposit Account 502624 and please credit any excess fees to such deposit account.

Respectfully submitted,

McDERMOTT WILL & EMERY LLP

/Astrid R. Spain/
Astrid R. Spain
Registration No. 47,956

11682 El Camino Real, Suite 400
San Diego, CA 92130
Phone: 858.720.3300 ARS:cjh
Facsimile: 858.720.7800
Date: December 28, 2009

Please recognize our Customer No. 41552 as our correspondence address.